large tasty insect, the future looks rosy. For its less fortunate sibling, an empty stomach in that first week of life may affect its decisions, and thus its ecology, for the rest of its time on earth. Experiences early in development are likely to have more effect than those later on, because the phenotype of a growing organism is increasingly hard to change in fundamental ways as development proceeds [2,3]. Nonetheless, even adult reptiles continue to flexibly adjust their tactics relative to the opportunities that they encounter. In species that experience variable food supply through space and time, life-history traits such as how fast you grow, how soon you mature, and how often you reproduce thereafter may be far from constant [14]. Perhaps reflecting the statistical concepts that are drummed into us during our training, scientists tend to focus on measures of central tendency on our datasets, and believe that our main job is to explain why average values for the traits we care about differ among things (such as species). If a snake was an ecological researcher, it would see the world very differently. For a species that can flexibly adjust its life-history traits to local conditions, the 'average' is almost meaningless — so our hypothetical scientific serpent would focus instead on the relationships between environmental conditions and phenotypic trait expression ('norms of reaction' in the jargon of the phenotypic plasticity enthusiasts [2]). Knowing the mean value for some species-specific trait would likely be informative only if one also knew values for the underlying environmental factors. Why obsess about averages, when those conditions likely apply only rarely and perhaps never? By analogy, the average reader of this article is likely to possess one testicle and one ovary, but few individuals will actually fit that description.

The plasticity exhibited by those young French lizards thus raises a broader issue. Does the highly inflexible 'constant-velocity' nature of our own physiology and life-history attract us to thinking in terms of averages? And how can we move away from that narrow perspective, to truly understand the exquisite sensitivity of other species, especially ectotherms, to environmental perturbations that appear absurdly trivial to us? Until we can imagine a world in which some of us mature at five years of age and others at 75, or where our wage fluctuates unpredictably between zero and a million dollars from one week to the next, we will struggle to grasp the reality of life for most of the species with which we share this planet. We have much to learn from reptiles, the paragons of plasticity.

References

1. Massot, M., and Aragon, P. (2013). Phenotypic resonance from a single meal in an insectivorous lizard. Curr. Biol. *23*, 1320–1323.
2. Falconer, D.S., and Mackay, T.F.C. (1996). Introduction to Quantitative Genetics (Essex, UK: Longman).
3. West-Eberhard, M.J. (2003). Developmental Plasticity and Evolution (Oxford, UK: Oxford University Press).
4. Moczek, A.P., Sultan, S., Foster, S., Ledon-Rettig, C., Dworkin, I., Nijhout, H.F., Abouheif, E., and Pfennig, D.W. (2011). The role of developmental plasticity in evolutionary innovation. Proc. R. Soc. B. *278*, 2705–2713.
5. Valenzuela, N., and Lance, V.A. (2004). Temperature Dependent Sex Determination in Vertebrates (Washington, DC: Smithsonian Institution Scholarly Press).
6. Shine, R., and Elphick, M. (2001). The effect of short-term weather fluctuations on temperatures inside lizard nests, and on the phenotypic traits of hatchling lizards. Biol. J. Linn. Soc. *72*, 555–565.
7. Shine, R., and Brown, G.P. (2002). Effects of seasonally varying hydric conditions on hatchling phenotypes of keelback snakes (*Tropidonophis mairii*, Colubridae) from the Australian wet-dry tropics. Biol. J. Linn. Soc. *76*, 339–347.
8. Clobert, J., Massot, M., and Le Galliard, J.-F. (2012). Multi-determinism in natal dispersal: the common lizard as a model system. In Dispersal Ecology Evolution, J. Clobert, M. Baguette, T. Benton, and J. Bullock, eds. (Oxford, UK: Oxford University Press), pp. 29–40.
9. Bleu, J., Massot, M., Haussy, C., and Meylan, S. (2011). Experimental litter size reduction reveals costs of gestation and delayed effects on offspring in a viviparous lizard. Proc. R. Soc. B *279*, 489–498.
10. Massot, M., Clobert, J., Montes-Poloni, L., Haussy, C., Cubo, J., and Meylan, S. (2011). An integrative study of ageing in a wild population of common lizards (*Lacerta vivipara*). Funct. Ecol. *25*, 848–858.
11. Greene, H.W. (1997). Snakes. The Evolution of Mystery in Nature (Berkeley, California: University of California Press).
12. Pough, F.H. (1980). The advantages of ectothermy for tetrapods. Am. Nat. *115*, 92–112.
13. Cox, C.L., and Secor, S.M. (2007). Effects of meal size, clutch, and metabolism on the energy efficiencies of juvenile Burmese pythons, *Python molurus*. Comp. Biochem. Physiol. A *148*, 861–868.
14. Madsen, T., and Shine, R. (2000). Rain, fish and snakes: climatically-driven population dynamics of Arafura filesnakes in tropical Australia. Oecologia *124*, 208–215.

School of Biological Sciences A08, University of Sydney, NSW 2006, Australia.
E-mail: rick.shine@sydney.edu.au

http://dx.doi.org/10.1016/j.cub.2013.06.004

Microtubule Motors: A New Hope for Kinesin-5 Inhibitors?

A new study demonstrates that two microtubule plus end-directed kinesins can oppose each other. The cause of this apparent contradiction is the specific orientation of microtubules on which each motor exerts its force.

Aaron Groen

The biopolar mitotic spindle is composed of different populations of microtubules. The kinetochore microtubules (K-MTs) are parallel bundles with minus-ends facing the spindle pole (Figure 1), while the non-K-MTs, or interpolar microtubules, are mostly anti-parallel in orientation [1,2]. Both sets of microtubules not only have unique underlying mechanisms of assembly but also specifically contribute to the balance of forces required for the steady-state bipolar spindle.

As reported in this issue of *Current Biology*, Sturgill and Ohi [3] find the plus end-directed kinesin Kif15 (kinesin-12) primarily localizes

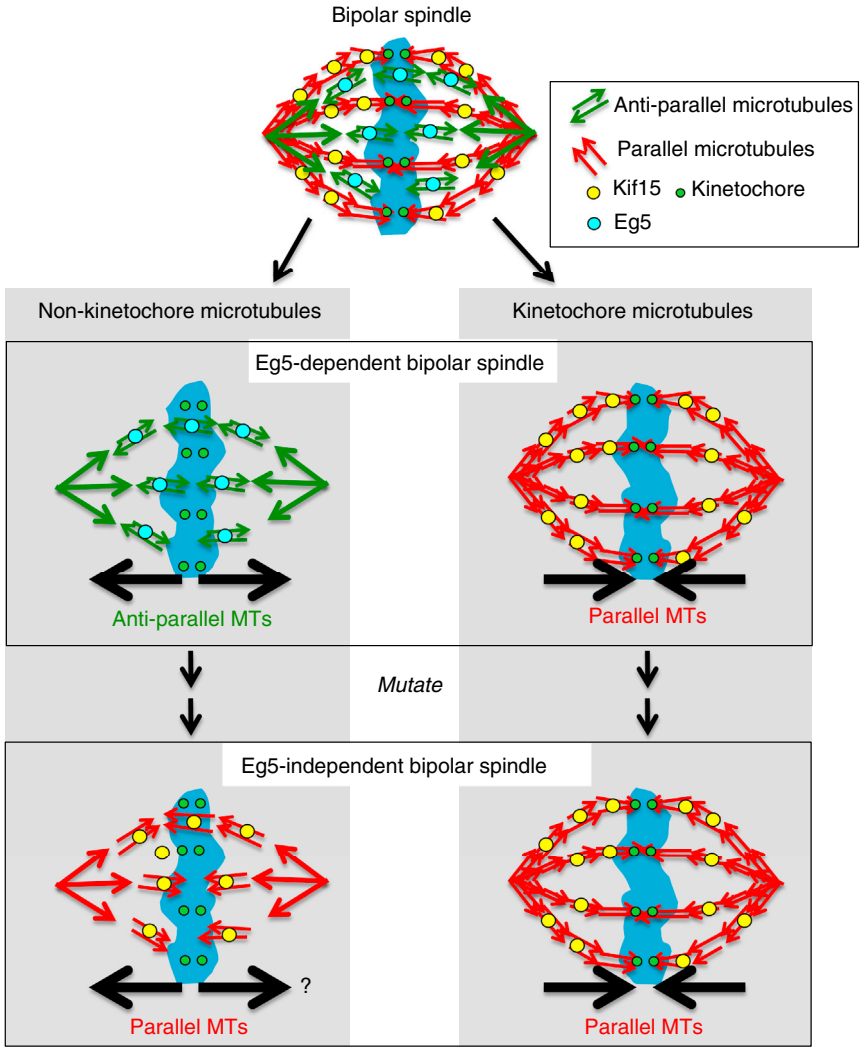

Figure 1. Two plus end-directed kinesins, two different functions.

In the mitotic spindle, Eg5 acts primarily on antiparallel microtubules, while Kif15 localizes and acts on parallel microtubules of the kinetochore fiber. The two kinesins produce opposing forces by acting on either antiparallel (Eg5) or parallel microtubules (Kif15). Sturgill and Ohi [3] develop an Eg5-independent cell line that relies on Kif15 and parallel microtubules to produce a bipolar spindle.

and exerts forces on parallel microtubules in kinetochore fibers (K-MTs), resulting in an inward force, while Eg5 (kinesin-5) exerts forces on anti-parallel non-K-MTs, resulting in an outward force (Figure 1). Unlike Eg5, forces produced by Kif15 are not critical for bipolar spindle assembly [3–5] but instead regulate steady-state spindle length.

The authors most importantly develop an Eg5-independent cell line requiring Kif15 instead of Eg5. In this case, Kif15 has become functionally equivalent to Eg5 by acquiring the ability to bind to non-K-MTs of the mitotic spindle and generate a force in the same direction as Eg5. Interestingly in this cell line, the non-K-MTs are predominantly parallel in orientation, suggesting Kif15 may bundle parallel microtubules and produce a force through the bundles either directly or through polymerization dynamics.

Kif15 is localized to the spindle microtubules by TPX2 [6]. Thus, it stands to reason that the higher recruitment of Kif15 on the Eg5-independent spindles may correlate with higher levels of TPX2. The recent implication of the TPX2/RanGTP pathway in Augmin-dependent microtubule branching presents the provocative idea that an increase in microtubule branches may provide the necessary substrates for the Kif15-dependent forces required to replace Eg5 [7].

One of the most salient aspects of this work is the potential to use Kif15 as an antimitotic drug target for cancer. Eg5 inhibitors have mostly failed in the clinic [8] and the work in this study may explain why. Like the cell lines developed in this study, Eg5 inhibitor-resistant tumor cells may use Kif15 instead. Thus, identifying a Kif15 inhibitor for use in cancer treatments in combination with Eg5 inhibitors could be valuable.

References

1. Toso, A., Winter, J.R., Garrod, A.J., Amaro, A.C., Meraldi, P., Andrew, D., and McAinsh, A.D. (2009). Kinetochore-generated pushing forces separate centrosomes during bipolar spindle assembly. J. Cell. Biol. *184*, 365–372.
2. McIntosh, J.R., and Landis, S.C. (1971). The distribution of spindle microtubules during mitosis in cultured human cells. J. Cell Biol. *49*, 468–497.
3. Sturgill, E.G., and Ohi, R. (2013). Kinesin-12 differentially affects spindle assembly depending on its microtubule substrate. Curr. Biol. *23*, 1280–1290.
4. Sawin, K.E., LeGuellec, K., Philippe, M., and Mitchison, T.J. (1992). Mitotic spindle organization by a plus-end-directed microtubule motor. Nature *359*, 540–543.
5. Tanenbaum, M.E., Macurek, L., Janssen, A., Geers, E.F., Alvarez-Fernandez, M., and Medema, R.H. (2009). Kif15 cooperates with eg5 to promote bipolar spindle assembly. Curr. Biol. *19*, 1703–1711.
6. Wittmann, T., Boleti, H., Antony, C., Karsenti, E., and Vernos, I. (1998). Localization of the kinesin-like protein Xklp2 to spindle poles requires a leucine zipper, a microtubule-associated protein, and dynein. J. Cell Biol. *143*, 673–685.
7. Petry, S., Groen, A.C., Ishihara, K., Mitchison, T.J., and Vale, R.D. (2013). Branching microtubule nucleation in Xenopus egg extracts mediated by augmin and TPX2. Cell *152*, 768–777.
8. Jones, R., Vuky, J., Elliott, T., Mead, G., Arranz, J.A., Chester, J., Chowdhury, S., Dudek, A.Z., Müller-Mattheis, V., Grimm, M.O., *et al*. (2013). Phase II study to assess the efficacy, safety and tolerability of the mitotic spindle kinesin inhibitor AZD4877 in patients with recurrent advanced urothelial cancer. Invest. New Drugs, http://dx.doi.org/10.1007/s10637-013-9926-y.

Department of Systems Biology, Harvard Medical School, Boston, MA 02115, USA.
E-mail: Aaron_Groen@hms.harvard.edu

http://dx.doi.org/10.1016/j.cub.2013.05.049